

IN THE SPECIFICATION:

Please replace paragraph [0077], with the following:

[0077]

The compounds described herein have asymmetric centers derived from the main backbone or side chain thereof; they are distinguished by absolute configuration, which is indicated using the prefix (R)-, (S)-, or (RS)-.

As used herein, the protective group represented by P_n, is a conventional protective group employed typically e.g. in peptide chemistry. Examples thereof include a benzyloxycarbonyl group, a t-butoxycarbonyl group, a ~~9-fluorenylmethylcarbonyl~~ 9-fluorenyloxymethylcarbonyl group, a benzyl group, a formyl group, and a trityl group for an amino group; a methyl group, an ethyl group, and a benzyl group for a carboxyl group; a formyl group, a trityl group, a benzyl group, and a t-butoxycarbonyl group for a nitrogen atom on an indole ring; and a benzyl group, a trityl group, and an acetyl group for the protective group of an oxygen atom in a hydroxylamine.

Please replace paragraph [0123], with the following:

[0123]

Among the above-described diabetic complications are coronary artery cardiac disease, peripheral circulatory disturbance, cerebrovascular disease, diabetic neurosis, diabetic retinopathy, diabetic arteriosclerosis, diabetic arthrosclerosis, cataract, diabetic retinopathy, diabetic coagulopathy, and diabetic osteopenia.

The composition of the invention is then described based on the medicinal composition. The medicinal composition of the invention may be orally or parenterally administered. For oral administration, it may be prepared in the form of hard capsules, soft capsules, tablets, granules, ~~granules~~, powders, subtle granules, pills, troches, active ingredient sustained-release preparations, elixirs, emulsions, syrups, solutions, suspensions, or the like.

Examples of the parenteral administration include injections such as drip infusion and intravenous, subcutaneous, and intramuscular injections, percutaneous administration using ointments or transdermal preparations, rectal administration using oil and fat suppositories, water-soluble suppositories, or suppositories, and administration using external preparations or ophthalmic solutions. The preparation can be easily carried out by a conventional method using a common carrier known in the pharmaceutical field.

When the medicinal composition of the invention is prepared in the form of oral administration, there may be employed widely used components for formulation such as a carrier, including, for example, a filler, an extender, a binder, a disintegrator, a disintegration inhibitor, a buffer, an isotonicizing agent, an emulsifier, a dispersant, a stabilizer, a coating agent, a surfactant, an absorption promoter, a humectant, a wetting agent, an absorbent, a lubricant, and an excipient. In addition, additives such as a coloring agent, a preservative, a flavor, a seasoning, and a sweetening agent may be optionally added.

Please replace paragraph [0164] with the following:

[0164]

(Example 69) Synthesis of (S)-2-amino-3-[1-(2-phenylethyl)-1H-indol-3-yl]-N-hydroxypropionamide (compound No. 61)

An operation similar to that in Example 68 was carried out using 31.7 ml (0.26 mmol) of phenethyl alcohol in place of 3-methyl-4-nitrobenzyl alcohol to provide 13.3 mg of the trifluoroacetate of the title compound as a pale yellow solid.

MS (Fab, Pos.): $m/z = 324$ $[M+H]^+$

(Example 70) Synthesis of 2-Boc-amino-4-(2-aminophenylcarbamoyl)-butyric acid hydroxamate O-supporting 2-chlorotrityl resin

In 15 ml of DMF was suspended 1.1867 g (equivalent to 1.07 mmol) of the resin obtained in Example 2, to which 347 mg (3.21 mmol) of o-phenylenediamine and 433.8 mg (3.21 mmol) of HOBt were then added. Thereto was added 0.37 ml (3.21 mmol) of DIC,

followed by shaking at room temperature for 3 days. After the end of reaction, the reaction liquid was filtered off, followed by washing with chloroform, DMF, and ethanol before drying to provide the title resin.

Please replace paragraph [0175] with the following:

[0175]

(Example 94) Synthesis of (S)-2-amino-4-(1-cyclohexyl-5,6-dimethyl-1H-benzimidazol-2-yl)-N-hydroxybutyramide (compound No. 84)

To 240 mg (equivalent to 0.46 mmol) of the resin obtained in Example 93 were added 1 ml of chloroform and 225.7 mg (2.30 mmol) of cyclohexanone, to which a solution consisting of 45 mg (0.72 mmol) of sodium cyanoborohydride dissolved in 1 ml of methanol and adjusted to a pH of 5 using acetic acid was further added, followed by stirring at room temperature for 3 days. After the end of reaction, the reaction liquid was filtered off, followed by washing with methanol, DMF, THF, chloroform, a chloroform/methanol solution, and ether before drying. ~~After the end of reaction, the reaction liquid was filtered off, followed by washing with methanol, DMF, THF, chloroform, a chloroform/methanol solution, and ether before drying.~~ Thereto was added 2 ml of acetic acid, followed by shaking at 60°C for 5 hours. The reaction liquid was collected by filtration, the resultant resin was washed with 2 ml of acetic acid, and the washings were added to the reaction liquid before concentration. The purification thereof was carried out using a normal phase solid-phase extraction column to provide an intermediate. The intermediate was dissolved in a 25% trifluoroacetic acid/chloroform solution before stirring for 2 hours, followed by distilling off the solution under reduced pressure. The solution obtained by filtration and the solution with which the resin had been washed were combined, from which the solvent was then distilled off. The residue was purified by a reverse phase system solid-phase extraction column to provide 27.6 mg of the trifluoroacetate of the title compound as a white solid.

MS (Fab, Pos.): $m/z = 345 [M+H]^+$

Please replace paragraph [0180] with the following:

[0180]

(Example 99-2) Synthesis of (S)-2-(cyclohexylmethyl-amino)-3-(4-nitrophenyl)-N-trityloxypropionamide

In 5 ml of DMF was dissolved 308.3 mg of the compound obtained in Example 99-1, to which 188.2 mg (0.862 mmol) of di-*t*-butyldicarbonate was then added, followed by stirring at 60°C for 17 hours. After the end of reaction, the solvent was distilled off, and the residue was dissolved in 3 ml of THF, to which 3 ml of methanol and 3 ml of 1 mol/l sodium hydroxide aqueous solution were then added, followed by stirring at room temperature for 2.5 hours. After the end of reaction, the solvent was distilled off, and the residue was dissolved in distilled water, which was then adjusted to a pH of 5 using a 1 mol/l hydrochloric acid aqueous solution. The resultant solution was extracted with chloroform, and the organic layer was dried over anhydrous sodium sulfate.

In 4.5 ml of chloroform was dissolved 149.1 mg (0.367 mmol) thereof, to which 105.9 mg (0.554 mmol) of WSCI hydrochloride and 106.7 mg (0.387 mmol) of O-tritylhydroxylamine were then added, followed by stirring at room temperature for one day. After the end of reaction, chloroform was added, followed by washing with a 1 mol/l hydrochloric acid aqueous solution, a 1 mol/l sodium hydroxide aqueous solution, and a saturated saline solution before ~~washing~~ drying the organic layer with anhydrous sodium sulfate. The solvent was distilled off, followed by purifying the residue using silica gel column chromatography (hexane/ethyl acetate) to provide 61.6 mg of a desired compound as a colorless, viscous material.

MS (Fab, Pos.): $m/z = 322 [M+H]^+$

$^1\text{H-NMR}$ (500 MHz, DMSO- d_6): $\delta = 0.51\text{-}0.70$ (2H, m), $0.96\text{-}1.12$ (4H, m), $1.37\text{-}1.49$ (2H, m), $1.49\text{-}1.60$ (3H, m), $1.77\text{-}1.83$ (1H, m), $1.85\text{-}1.91$ (1H, m), 2.54 (2H, d, $J = 6.8$ Hz), 3.06 (1H, dd, $J = 7.1, 6.6$ Hz), $7.25\text{-}7.38$ (17H, m), 8.03 (2H, d, $J = 8.8$ Hz).

Please replace paragraph [0312] with the following:

[0312]

(Example 138-4) Synthesis of (R)-2-amino-4-(1-phenyl-5,6-dimethyl-1H-benzimidazol-2-yl)-N-hydroxybutyramide (compound No. 120)

To 0°C was cooled 178 mg (0.261 mmol) of the compound obtained in Example 138-3, to which 2 ml of 4 mol/l hydrogen chloride/dioxane was then added, followed by stirring at room temperature for 4 hours. After the end of reaction, the solvent was distilled off, and the solid was washed with chloroform/hexane, followed by further repeating the washing with hexane before vacuum drying to provide 95.9 mg of the hydrochloride of the title compound as a white solid.

MS (Fab, Pos.): $m/z = 339 [M+H]^+$

$^1\text{H-NMR}$ (500 MHz, $\text{DMSO-d}_6 + \text{D}_2\text{O}$) $\delta = 2.26$ (1H, dd, $J = 8.2, 15.4$ Hz), 2.29 (1H, dd, $J = 8.2, 15.4$ Hz), 2.32 (3H, s), 2.40 (3H, s), 2.97-3.02 (2H, m), 3.65-3.75 (1H, m), 7.07 (1H, s), 7.61-7.70 (3H, m), 7.71-7.80 (3H, m).

Please replace paragraph [0389] with the following:

[0389]

(Example 162) Synthesis of (S)-2-amino-3-[1-(3-methylbutyl)-1H-indol-3-yl]-N-hydroxypropionamide (compound No. 144)

(Example 162-1) Synthesis of (S)-2-t-butoxycarbonylamino-3-[1-(3-methylbutyl)-1H-indol-3-yl]propionic acid benzyl ester

In 10 ml of acetone was dissolved 530 mg (1.35 mmol) of commercial N^α -Boc-tryptophan benzyl ester, to which 1.00 ml of ~~iodohexane~~ 3-methylbutylbromide was then added. Thereto was added 278 mg (0.853 mmol) of cesium carbonate, followed by stirring at 60°C for 2 days. After the end of reaction, the solvent was distilled off, followed by adding hexane and ethyl acetate to the residue before removing the insoluble matter by filtration. The solvent was distilled off, followed by purifying the residue using silica gel column

chromatography (hexane/ethyl acetate) to provide 126 mg of the title compound as a colorless, viscous oil.